IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4326
Ho *et al.*	Art Unit: 1651
Application No.: 09/960,244	Examiner: Lankford Jr., Leon B.
Filed: Sept. 21, 2001	Atty. Docket: 2560.0020000/JAG/DOS
For: **Cell Populations Which Co-Express CD49c and CD90**	

Amended Brief on Appeal Under 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In response to a Notification of Non-Compliant Appeal Brief and the Advisory Action (both mailed Dec. 24, 2009) wherein the Examiner refused to enter Appellants' previously requested amendment, Appellants submit herewith an Amended Brief wherein the *Claims Appendix* has been corrected to show claim 97 as previously presented (*i.e.*, prior to Appellants' requested Amendment Under 37 C.F.R. § 1.116). References to claim 97 have also been amended as necessary elsewhere herein.

The presently Amended Brief is submitted herewith on Monday, Jan. 25, 2010 as Jan. 24, 2010 was a Sunday. Accordingly, it is not believed that extensions of time are necessary in filing the presently Amended Brief. However, if extensions of time are necessary for further consideration of this Appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 19-0036.

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I. Real Party In Interest (37 C.F.R. § 41.37(c)(1)(i))

The real party in interest in this appeal is Garnet BioTherapeutics Inc. ("Garnet")(formerly Neuronyx, Inc.), 1 Great Valley Parkway, Suite 12, Malvern, PA 19335, the assignees of record.

II. Related Appeals and Interferences (37 C.F.R. § 41.37(c)(1)(ii))

There are currently no other prior and pending appeals, interferences or judicial proceedings known to appellant, the appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. However, during the expected pendency of this Appeal, Appellants are contemplating filing an appeal in related U.S. Patent Application No. 11/054,824, which is a divisional of the subject application in this appeal, and in which a final office action was mailed on April 3, 2009. Appellants are also contemplating filing an appeal in U.S. Patent Application No. 10/251,685, which discloses and claims related subject matter, which is assigned to the real party in interest in the present appeal, and in which a final office action was mailed on April 10, 2009.

Reference to related patent applications or proceedings is not meant to be an admission that any related proceeding directly affects, is directly affected by, or has a bearing on the Board's decision in the presently pending appeal.

Appellants note that on June 16, 2009 a Petition under 37 C.F.R. § 1.181 was submitted requesting rescission of a requirement by the Examiner to cancel allegedly new subject matter in an amendment submitted by the Appellants on March 5, 2008. On July 14, 2009 the U.S.P.T.O. mailed a decision denying Appellants' petition.

III. Status of Claims (37 C.F.R. § 41.37(c)(1)(iii))

Claims 14, 21, 25, 26 and 97 are pending.

Claims 1-13, 15-20, 22-24, and 27-96 are canceled.

Claims 14, 21, 25, 26 and 97 are rejected.

Claims 14, 21, 25, 26 and 97 are being appealed.

Independent Claim 14 and dependent claims 25 and 26 stand or fall together based on the arguments presented herein. Dependent claim 21 and independent claim 97 are each appealed separately and each stands or falls separately based on the arguments presented herein.

IV. Status of Amendments (37 C.F.R. § 41.37(c)(1)(iv))

On June 16, 2009 Appellants submitted a Petition under 37 C.F.R. § 1.181 requesting the Director to review and rescind a requirement by the Examiner to cancel allegedly new matter that was submitted on March 5, 2008 for amendment of a portion of the specification. This Petition was denied in a decision mailed on July 14, 2009.

Subsequently, on the same date of filing the present appeal, Appellants submitted a request for amendment of the specification pursuant to 37 C.F.R. § 1.116(b)(3) to cancel the allegedly new matter which was objected to, for the first time, in the Examiner's Final Office Action mailed on March 16, 2009.

Appellants also submitted a request for amendment of claim 97 pursuant to 37 C.F.R. § 1.116(b)(2) (as discussed further herein) in order to present this rejected claim in better form for consideration on appeal (in view of objections made by the Examiner in the Final Office Action mailed on March 16, 2009).

On December 24, 2009 the Examiner mailed a Notification of Non-Compliant Appeal Brief and an Advisory Action wherein he refused to enter Appellants' August 17, 2009 Amendments Under 37 C.F.R. § 1.116.

V. Summary of Claimed Subject Matter (37 C.F.R. § 41.37(c)(1)(v))

Appellants' invention, as recited by independent claims 14 and 97, is directed to isolated populations of primary, non-immortalized, extensively self-renewing cells derived from human bone marrow that exhibit a unique phenotype characterized, in part, by the ability to maintain a constant population doubling rate through an unexpectedly large number of cell doublings *in vitro,* and by maintaining the ability (throughout such large number of cell doublings) to enhance regeneration of damaged organs and tissues. The claimed cell populations are characterized by cell-surface co-expression of protein markers CD49c and CD90. The cells are also characterized by expression of a variety of additional cell-surface markers and secretion of numerous therapeutically beneficial cytokines and growth factors.

Cell populations of the invention are unlike other previously isolated bone marrow-derived (BM) cells and, in particular, unlike previously isolated BM mesenchymal stem cells (MSCs). Previously isolated BM mesenchymal stem cells exhibit a characteristic and

predictable profile of limited and continually slowing *in vitro* growth and proliferation resulting from the early onset of senescence and/or differentiation after a limited number of passages in culture. This characteristic growth profile of previously isolated BM mesenchymal stem cells is evidenced by continuously-increasing cell population doubling times observed in the cell populations after each *in vitro* passage.

In contrast to such previously identified BM cells, the claimed cell populations are characterized by their ability to proliferate *at a rapid and constant cell population doubling rate through numerous population doublings*, without exhibiting replicative senescence through more than 50 population doublings. *See e.g.*, **Exhibit 1**; Specification, Figures 3 & 4. The constant population doubling rate exhibited by cell populations of the invention is advantageous and significant because it demonstrates the phenotypic stability of the cells *in vitro* and shows that the cells have not begun to senesce or terminally differentiate. Moreover, the constant population doubling rate, without concurrent senescence or terminal differentiation, is necessary for the large-scale production of therapeutically useful cells with a demonstrated, highly stable phenotype from a small amount of starting material (*i.e.*, a bone marrow aspirate from a single donor).

In another embodiment, Appellants' invention, recited by dependent claim 21, is directed to cell populations of claim 14 that express limited quantities of p53 and p21 after about 20 to about 50 cell population doublings. In particular, cell populations according to this embodiment of the invention express up to about 3000 transcripts of p53 and up to about 20,000 transcripts of p21, as measured relative to the expression of 10^6 transcripts of 18s rRNA. Limited expression of p53 and p21 is a significant attribute of cell populations of the invention because it shows that the cells are still undergoing active cell division without having begun to terminally differentiate or senesce (*i.e.*, die-off).

In another embodiment, Appellants' invention, recited by dependent claim 25, is directed to cell populations of claim 14 that further do not express either, or both of, the hematopoietic cell surface markers CD34 and CD45. Lack of expression of hematopoietic cell surface markers is a significant attribute of cell populations of the invention because the majority of cells present in bone marrow *are* hematopoietic cells and hematopoietic progenitor cells. Thus, lack of CD34 and/or CD45 expression indicates the isolation of a *non*-hematopoietic cell population.

In another embodiment, Appellants' invention, recited by dependent claim 26, is directed to cell populations of claim 14 that further express at least one trophic factor (*i.e.*, a naturally occurring molecule that promotes cell growth, proliferation, and/or survival). The trophic factor

or factors expressed is/are one or more of brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), nerve growth factor (NGF) and macrophage chemoattractant protein-1 (MCP-1). Expression of one or more of these trophic factors is a significant attribute of cell populations of the invention because factors such as these indicate that the cell populations produce therapeutically beneficial compounds that have value in treating, for example, damaged organs or tissues.

In another embodiment, Appellants' invention is directed to cell populations prepared using methods recited in independent, product-by-process claim 97. In particular, isolated cell populations of the invention may be obtained by incubating a starting population of human bone marrow cells under low oxygen conditions, allowing cells in the starting population to adhere to a tissue culture-treated surface and form colony forming units, then passaging the adherent colony forming units of cells at seeding densities of less than 2500 cells/cm^2. The claimed, isolated population of cells obtained in this manner are greater than about 91% positive for co-expression of CD49c and CD90, and the cell populations are able to maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

Critical for isolating the unique cell populations of the invention is the manner in which the cell populations are initially isolated, cultured and expanded. In particular, heterogeneous cell populations are obtained from a sample of human bone marrow (for example a bone marrow aspirate) and the heterogeneous mixture of bone marrow cells are allowed to adhere to a tissue culture-treated surface *under low oxygen conditions*. Once adherent colony forming units are produced, the cells are passaged *at low cell seeding densities*.[1] Thus, by isolating and passaging the cells under the combination of *low oxygen conditions* and at *low cell seeding densities*, it as been discovered that claimed cell populations can be maintained in culture with consistent population doubling rates of less than about 30 hours even after 30 or more population doublings.

The ability to propagate cell populations of the claimed invention provides a substantial and significant advantage over cell populations initially obtained in a similar manner (as has been described in the prior art) *but without the combination of low oxygen and low cell seeding density conditions.* Such prior art cell populations are not able to maintain consistent cell population doubling rates with continued cell doublings. In other words, for prior art bone

[1] For example, as described in the specification, seeding densities of "less than about 2500 cell/cm^2, preferably less than about 1000 cells/cm^2, and most preferably less than about 100 cells/cm^2. In a particular embodiment, the initial cell density in the expansion step is between about 30 cells/cm^2 to about 50 cells/cm^2. *See*, **Exhibit 1**; specification, page 12, lines 4-9.

marrow-derived cell populations grown under standard oxygen conditions (usually standard atmospheric conditions supplemented with 5% CO_2) and passaged at higher cell seeding densities, as the number of cell passages increases the cell population doubling times become longer and longer. In contrast, bone marrow derived cell populations of the present invention are able to consistently maintain a population doubling rate of less than about 30 hours after 30 (or more) cell doublings.

The ability of a cell population to maintain a consistent population doubling rate is an important and significant phenotypic marker because when *in vitro*-passaged cell populations exhibit progressively longer doubling times (under consistent culture conditions) this change represents an irreversible change in cell population phenotype. *See*, **Exhibit 2**; First Kopen Declaration, Section E.2(A), pages 21-23. In other words, cell populations that have acquired progressively slower population doubling times cannot be induced to revert back to their initial shorter population doubling times. This point is important because it indicates the bone marrow-derived cell populations isolated by others that are described as gaining increasingly longer *in vitro* cell population doubling times are undergoing changes that cannot be reversed. In other words, such cell populations are progressively passing "points of no return" with respect to reverting back to an initial, shorter, cell population doubling times. This is demonstrated as attested to in the First Kopen Declaration which explained:

> All living cells possess a lower limit on population doubling time such that they can only grow as fast as the mechanics of cell division will allow...
>
> "[P]opulation doubling time" or T_d is calculated by measuring the time required for an *entire population* of cells to multiply by a factor of two (*e.g.*, for a population of 1 million cells to become 2 million cells). Population doubling time does not reflect the actual time required for each individual cell in the population to divide...Since T_d reflects the *average* time it takes for a population of cells to divide, as cells in the population begin to leave the cell cycle, the T_d will grow increasingly longer...
>
> It is well established that when mammalian cells leave the cell cycle (*i.e.*, enter G_0 phase), they either reach a state of terminal differentiation or senesce and die. Thus, when a population of anchorage-dependent cells maintained under constant culture conditions begins to demonstrate increasingly longer T_d with each passage *in vitro*, this indicates that an increasingly larger percentage of the cell population has left the cell cycle and, as a result, the population as a whole can no longer revert back to a substantially faster T_d. For example, Lennon *et al.* (Jour. Cell. Physiol., 187:345-355 (2001); attached herewith as Exhibit E)

> have shown that rat bone marrow mesenchymal cells cannot be switched back and forth between optimal and less optimal growth conditions and also continue to maintain their initial lowest population doubling rate. Thus, when experimental cells in Lennon *et al.* were initially cultured under less favorable growth conditions (such as high oxygen tension), then switched to growth conditions that favor faster growth (such as low oxygen tension), the cells fail to re-acquire the rapid population doubling times exhibited by control cultures maintained, in parallel, under optimal growth (*i.e.*, low oxygen) conditions.
>
> Thus, if one were to start with a relatively pure cell population with an average T_d of less than about 30 hours and then cultured these cells *in vitro* such that the cells begin to undergo asymmetric division wherein a proportionally greater number of cells enter G_0 with each round of cell division, the population would quickly begin to demonstrate a T_d that exceeds the initial 30 hour population doubling time. This change in T_d would, therefore, indicate that the phenotype of the cells in the cell population is changing with each new cell passage.
>
> ...[Hence, T_d can] be used as a surrogate marker for cell differentiation because as the cell population's doubling time continues to slow down, more cells are leaving the cell cycle, and by definition, are therefore "different" from those still capable of self renewal...
>
> In sum, T_d can be considered a phenotypic measure of a cell population's level of homogeneity as well as its potential, or lack thereof, for re-entry into the cell cycle.

See, **Exhibit 2**; First Kopen Declaration, Section E.2(A), pages 21-23.

Hence, the ability to culture cell populations of the present invention with consistently rapid cell population doubling rates over a large number of population doublings is significant for at least two reasons. First, the consistent cell population doubling rate demonstrates that these *in vitro* cultured, primary cell populations of the invention are *maintaining a consistent and stable* phenotype. *See*, **Exhibit 2**; First Kopen Declaration, Section E.2(A), pages 21-23. For example, the consistent cell population doubling rate shows that cells within the cell population are a homogenous (as opposed to heterogeneous) population of cells which are neither entering the G0 phase of the cell cycle nor are they senescing (dying) at an appreciable rate. *Id.* Second, the ability to culture a stable, uniform population of primary cells over a large number of cell doublings is significant because it means that a very large number of stable and phenotypically identical cells can be produced from a small sample of bone marrow from a single donor in a very short time. In fact, it is possible to generate up to $1x10^{17}$ cells from 25

milliliters (mLs) of single donor bone marrow aspirate following four cell passages (*i.e.*, four expansions producing ~35-40 population doublings) in less than 60 days. *See*, **Exhibit 1**; Specification, Example 4, page 29, lines 21-22; *see also* Figure 4. This amounts to generation of $4x10^{15}$ cells/mL ($1x10^{17} \div 25 = 4x10^{15}$) or 4,000,000,000,000,000 cells/mL or 4,000 trillion cells/mL of donor sample produced in less than 2 months with only 4 cell culture passages.[2]

Claims 14, 21, 25, 26 and 97 are supported throughout the specification, *e.g.*, as exemplified by Table 1:

Table 1: Illustrative Support in the Specification for the Pending Claims

Claim No(s).	Illustrative Support from the Specification
14	Page 2, lines 2-3; page 7, lines 8-10; page 10, lines 17-18, page 25, lines 11-12; page 27, lines 1-8 and lines 11-12; page 28, lines 1-6; page 29 line 25 to page 30, line 2; Figure 1B; Figure 2B; and Figure 4.
21	Page 9, lines 14-25.
25	Page 12, lines 24-28.
26	Page 13, lines 3-11.
97	Page 7, lines 8-10; page 11, lines 3-6 and lines 12-21; page 12, lines 4-7; page 14, lines 16-23; page 15, lines 6-8; page 28, lines 5-6; page 29, line 25 to page 30, line 2 (*see also*, Examples 1-3; page 25, line 9 to page 29, line 6).

[2] In contrast "MSC" cells, as taught in Bruder (describing the same cells of Haynesworth), require *15 passages* performed approximately every 5 to 10 days (totaling *between 75 and 150 days in culture*) to obtain ~38 population doublings. *See,* **Exhibit 12**; Bruder, page 284, left col., last paragraph to page 285, left col., last paragraph; and, Figure 5.

VI. Grounds of Rejection to be Reviewed on Appeal (37 C.F.R. § 41.37(c)(1)(vi))

A. Rejections based on 35 U.S.C. § 102(b).

The sole remaining ground of rejection applied to *all* of the pending claims is inherent anticipation under 35 U.S.C. § 102(b).

Pending claims 14, 21, 25, 26 and 97 stand rejected under 35 U.S.C. § 102(b) as allegedly inherently "anticipated by Haynesworth et al. (1998, U.S. Patent 5,733,542) taken in light of Pittenger et al. (1999, Science 284: 143-147), Woodbury et al. (2000, Journal of Neuroscience Research 61:364-370), and Lee et al. ([2004], Hepatology 40: 1275-1284)."[3] *See*, **Exhibit 3**; Final Office Action, page 7.

Each of the above-cited references is included herewith as an Exhibit and is referred to hereinafter by name of the first named inventor or author. Accordingly, "Haynesworth" (U.S. Patent 5,733,542) is included as **Exhibit 4**; "Pittenger" (Pittenger *et al.*, Science 284: 143-147 (1999)) is included as **Exhibit 5**; "Woodbury" (Woodbury *et al.*, Journal of Neuroscience Research 61:364-370 (2000)) is included as **Exhibit 6**; and "Lee" (Lee *et al.*, Hepatology 40: 1275-1284 (2004)) is included as **Exhibit 7**.

Haynesworth is cited by the Examiner as teaching "a population of mesenchymal stem cells (MSCs) isolated from human adult bone marrow." *See*, **Exhibit 3**; Final Office Action, page 7.

Pittenger is cited by the Examiner as "evidence that the MSCs of Haynesworth et al. can differentiate to various mesodermal cell lineages, including bone, cartilage, and adipose." *See*, **Exhibit 3**; Final Office Action, page 7.

Woodbury is cited as "evidence that the MSCs of Haynesworth et al. can differentiate to neurons." *See*, **Exhibit 3**; Final Office Action, page 7.

Lee is cited as "evidence that the MSCs of Haynesworth et al. can differentiate to hepatocytes." *See*, **Exhibit 3**; Final Office Action, page 7.

B. Rejection based on 35 U.S.C. § 112, first paragraph.

Claim 97 stands singularly rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner alleges

[3]The Examiner incorrectly cited Lee *et al.* as published in 2000, however, Lee *et al.*, Hepatology 40: 1275-1284, was actually published in 2004.

that the specification does not contain written description support for the limitation of "a seeding density of 'less than about 2500 cells/cm^2.'" *See*, **Exhibit 3**; Final Office Action, page 5.

C. Rejection based on 35 U.S.C. § 112, second paragraph.

Claim 97 stands singularly rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner alleges the metes and bounds of the limitation for a "low oxygen" condition are unclear. *See*, **Exhibit 3**; Final Office Action, pages 5-6.

D. Objection based on 35 U.S.C. § 132(a).

Appellants' amendment submitted on June 16, 2009 stands objected to as allegedly introducing new matter into the disclosure. In particular, an amendment introduced to provide further clarity in the specification has been objected to as allegedly "changing the description of the invention." *See*, **Exhibit 3**; Final Office Action, page 6.

E. Provisional Double Patenting Rejection

The Examiner states a provisional non-statutory double patenting rejection of claims 14, 21, 25, 26 and 97 based on the co-pending, *later filed* 10/251,685 application. *See*, **Exhibit 3**; Final Office Action, pages 11-13.

VII. Argument (37 C.F.R. § 41.37(c)(1)(vii))

A. Procedural Background

The present appeal is necessary to address one fundamental objection asserted by the Examiner under 35 U.S.C. § 102(b). This objection is founded on the Examiner's persistent, but mistaken, contention that the presently claimed cell populations are the same as MSCs isolated and identified by others in the prior art. More particularly, the present appeal follows eight years of prosecution during which the examiner first maintained, then dropped,[4] and now again maintains that the presently claimed cell populations are the same as previously isolated "Mesenchymal Stem Cells."

[4] Notice of Allowance mailed December 15, 2005 and Issue Fee paid February 2, 2005.

During the course of prosecution, in earnest attempt to bring claims in the present application to allowance, Appellants have transacted in: four rounds of non-final rejections and responses; two rounds of final rejections and responses, *plus* the presently pending final rejection; one request for continued examination; one notice of allowance; one issue fee payment; one withdrawal of the notice of allowance (prior to which the issue fee had been paid); more than a year suspension of prosecution due to a potential interference which was never declared; and, four interviews with the Examiner (including two interviews with the Examiner and his Supervisor (Michael Wityshyn).

During this time, Appellants have supplied evidence and explanations based on numerous supporting documents, affidavits, and exhibits in support of the claimed invention. In particular, Appellants have supplied two separate affidavits by Dr. Gene Kopen with 41 total pages of testimony and 7 different evidentiary exhibits. (These affidavits are referred to herein as the "First Kopen Declaration" (**Exhibit 2;** *including Exhibits A-D referenced therein*) and the "Second Kopen Declaration" (**Exhibit 8;** *including Exhibits A-E referenced therein*); these were submitted in the present application on May 18, 2007 and March 5, 2008, respectively.)

Accordingly, in this Appeal the Appellants again provide evidence, explanations, and affidavits demonstrating the renewed (and previously asserted) errors in the Examiner's position.

This evidence, explanations, and affidavits provided herewith, provide uncontroverted factual evidence that the claimed invention is not anticipated by the prior art. Although the claims have been amended and restated numerous times in attempt to satisfy the Examiner's contentions, Appellants have consistently pointed to strong factual evidence to establishing patentability of the invention.

B. Legal Background

To anticipate a claim under 35 U.S.C. § 102(b), a prior art reference normally needs to disclose each and every limitation of the claim. However, a prior art reference can anticipate when the claim limitations not expressly found in that reference are nonetheless inherent in it. *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates."). As stated by the Federal Circuit in *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1993), "[a] claim is anticipated and therefore invalid only when a single prior art reference discloses each and every limitation of the claim. . . . The disclosure

need not be express, but may anticipate by inherency where it would be appreciated by one of ordinary skill in the art."

A required element of inherent anticipation is that the "missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002); *see also Electro Medical Sys., S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1052 (Fed. Cir. 1994) ("'The mere fact that a certain thing *may result* from a given set of circumstances is insufficient to prove anticipation.' . . . [The challenger] was required to prove that an unpressurized flow is necessarily present in the [prior art] disclosure, and that it would be so recognized by persons of ordinary skill . . . .") (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). Hence, the judicially created doctrine of inherent anticipation requires that a rejection based on inherent anticipation cannot be based on mere possibilities or probabilities; the missing matter must necessarily flow from the prior art.

Inherency of a limitation in a reference is a question of fact. *See Telemac Cellular Corp. v. Top Telecom, Inc.*, 247 F.3d 1316, 1327 (Fed. Cir. 2001). A feature may be inherent if "the prior art necessarily functions in accordance with, or includes, the limitations." *Id.* at 1328 (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362 (Fed. Cir. 1999). To serve as an anticipatory reference when the reference is silent about the asserted inherent characteristic, such a gap in the reference can be filled with recourse to extrinsic evidence, provided such evidence makes clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *See Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1268; *see also In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

The M.P.E.P. also clearly explains the requisite burden of proof that an Examiner must provide in asserting a rejection based on inherent anticipation. In particular, the M.P.E.P. states:

> **Requirements of Rejection Based on Inherency; Burden of Proof**
>
> IV. EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY
>
> The fact that a certain result or characteristic *may* occur or be present in the prior art *is not sufficient* to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily

> present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "*To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.* ***Inherency, however, may not be established by probabilities or possibilities.*** *The mere fact that a certain thing may result from a given set of circumstances is not sufficient.*' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).
>
> * * *
>
> In relying upon the theory of inherency, *the examiner must provide a basis in fact and/or technical reasoning* to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. Apages & Inter. 1990).

See, M.P.E.P. § 2112, IV (italics emphasis added; bold emphasis in original).

In the present appeal, Appellants submit that the Examiner has not established a *prima facie* case of inherent anticipation. Moreover, and to the contrary, Appellants have previously, and again herein, provide evidence that the allegedly anticipatory prior art reference (*i.e.*, Haynesworth) does not inherently anticipate the claimed invention at issue.

C. Claims 14, 21, 25, 26 and 97 are not anticipated by the cited references

1. Summary of the Cited References

a) Haynesworth (U.S. Patent No. 5,733,542)

Haynesworth is cited by the Examiner as teaching "a population of mesenchymal stem cells (MSCs) isolated from human adult bone marrow." *See*, **Exhibit 3**; Final Office Action, page 7. Haynesworth teaches methods of using "mesenchymal stem cells (MSCs)" to enhance bone marrow engraftment and regeneration of bone marrow by administration of "MSCs." (**Exhibit 4**, throughout). *Haynesworth itself does not describe any particular cell markers expressed, or not expressed, by the MSCs used therein.*

Haynesworth, however, is one member of a patent family commonly assigned to Osiris Therapeutics Inc. (Baltimore, MD). This patent family also has commonly named inventors Stephen E. Haynesworth and Arnold I. Caplan. These facts are significant because, although the specification of Haynesworth does not describe cell surface markers expressed by the MSCs isolated and cultured according to the methods therein, other members in the Haynesworth patent family *do* describe "MSC" cell surface markers.

As such, Haynesworth teaches:

> The present invention is directed to various methods and devices for using mesenchymal stem cells (MSCs) to enhance bone marrow engraftment. Mesenchymal stem cells are the formative pluripotent blast cells found in the bone that are capable of differentiating into any of the specific types of connective tissues (*i.e.*, the tissues of the adipose, areolar, osseous, cartilaginous, elastic, and fibrous connective tissues) depending upon various environmental influences. Although these cells are normally present at very low frequencies in bone marrow and other mesenchymal tissues, the inventors of the present invention have discovered a process for isolating, purifying, and greatly replicating the mesenchymal stem cells in culture, *i.e. in vitro*. This discovery is the subject of co-pending *U.S. patent application Ser. No. 193,262*, filed Feb. 8, 1994.

See, **Exhibit 4;** Haynesworth, col. 1, lines 17-31 (emphasis added).

Indeed, Haynesworth (filed Jan. 24, 1995) claims benefit of priority as a continuation-in-part of the cited *U.S. patent application Ser. No. 193,262* (which later issued with first named inventor Arnold Caplan as U.S. Patent No. 5,486,359; hereinafter "Caplan '359" (**Exhibit 10**)). Like Haynesworth, another related patent, U.S. Patent No. 5,811,094 (filed Apr. 4, 1994) with first inventor Arnold Caplan (hereinafter "Caplan '094" (**Exhibit 11**)), is also a continuation-in-part of Caplan '359.

Caplan '094, Caplan '359, and Haynesworth each describe isolation and cultivation of MSCs using the same methods. *Compare*, Haynesworth, Example 1, col. 3, line 20 to col. 4, line 51 (**Exhibit 4**) *versus* Caplan '359, col. 16, line 9 to col. 17, line 43 (**Exhibit 10**) *and* Caplan '094, col. 18, line 53 to col. 20, line 14 (**Exhibit 11**); *see also,* Kopen Second Declaration, Section B.1., pages 3-4 (**Exhibit 8**).

Unlike the Haynesworth patent specification, however, the Caplan '094 and Caplan '359 patent specifications provide additional (and highly relevant) information about characteristics of Haynesworth's "MSCs." For example, Caplan '094 provides highly relevant information regarding expression of cell surface markers which is not included in the Haynesworth specification. *See*, **Exhibit 11;** Caplan '094, Example 4, cols. 37-39, *esp.* Table 5. In this regard, Appellants note that Caplan '094 teaches that the "MSCs" described therein (which are the same MSCs as those of Haynesworth) are *negative* for expression of cell surface marker CD44. Additionally, Caplan '094 and '359 teach that the "MSCs" of Haynesworth are present in bone marrow in "minute amounts" at frequencies in the range of 1 "MSC" for every 10,000 to

2,000,000 cells. *See*, **Exhibit 11;** Caplan '094, col. 6, lines 19-24 *and* **Exhibit 10;** Caplan '359, col. 4, lines 24-34. The significance of these and other characteristics of the "MSCs" of Haynesworth compared to the claimed cell populations are discussed further below.

b) Pittenger et al. (Science 284: 143-147 (1999))

Pittenger is cited by the Examiner as "evidence that the MSCs of Haynesworth *et al.* can differentiate to various mesodermal cell lineages, including bone, cartilage, and adipose." *See*, **Exhibit 3**; Final Office Action, page 7. Pittenger (**Exhibit 5**) is a journal publication with the majority of authors employed by Osiris Therapeutics Inc. (though Pittenger does not list Haynesworth or Caplan as authors). Pittenger (published April 2, 1999) describes the multilineage differentiation potential of "hMSCs" (human "MSCs") isolated from human bone marrow by density gradient centrifugation. *See*, **Exhibit 5**; Pittenger, page 143, last paragraph to page 144, first paragraph. Cells within populations of the MSCs described in Pittenger could be induced (by exposure to various supplements) to become adipocyte-, chondrocyte-, or osteocyte-like cells. *See*, **Exhibit 5**; Pittenger, throughout.

Pittenger also describes a variety of cell surface markers expressed by the MSCs used therein. In particular, Appellants note that Pittenger describes MSCs as CD106 and CD62L positive. *See,* **Exhibit 8**; Second Kopen Declaration, Section C, pages 12-13 (including Exhibit E; "Supplemental Web data" cited in Pittenger. The significance of this compared to attributes of the claimed cell populations is discussed further below.

c) Lee et al.(Hepatology 40: 1275-1284 (2004))

Lee is cited by the Examiner as "evidence that the MSCs of Haynesworth *et al.* can differentiate to hepatocytes." *See*, **Exhibit 3**; Final Office Action, page 7. Lee is a 2004 journal publication by a group of scientists working in Taiwan with no apparent connection to Osiris Therapeutics, Inc. Lee describes the ability of "MSCs" to differentiate into hepatocyte-like cells. *See*, **Exhibit 7**; Lee, Abstract, page 1275 and throughout. The MSCs in Lee were isolated from human bone marrow aspirates, first by antibody-based immunodepletion of cells positive for expression of CD3, CD14, CD19, CD38, CD66b and glycophorin-A, followed by gradient centrifugation and single cell plating. *Id.* at page 1276, left col. last paragraph to right col., first paragraph.

Lee also describes the MSCs isolated therein as negative for expression of CD13 and as having population doubling times of between 40 to 52 hours. *See*, **Exhibit 7**; Lee, page 1278, right col. and page 1278, right col., 1st paragraph. The significance of these characteristics compared to attributes of the claimed cell populations are discussed further below.

d) Woodbury et al. (Journal of Neuroscience Research 61:364-370 (2000))

Woodbury is cited by the Examiner as "evidence that the MSCs of Haynesworth et al. can differentiate to neurons." *See*, **Exhibit 3**; Final Office Action, page 7.

Woodbury is a 2000 journal publication by a group of scientists from UMDNJ-Robert Wood Johnson Medical School (Piscataway, NJ) and MCP Hahnemann University (Philadephia, PA), with no apparent connection to Osiris Therapeutics, Inc. Woodbury describes the ability of rat and human "MSCs" to differentiate into neuron-like cells. The human "MSCs" described in Woodbury are the same as those described in Azizi *et al.*, *Proc Natl Acad Sci USA*. 95:3908-3913 (1998) (hereinafter "Azizi" **(Exhibit 9)**). This is evidenced by attribution in Woodbury to Azizi that the "hMSCs [human MSCs] were isolated from a healthy adult donor and grown *in vitro* (Azizi et., 1998)."

Azizi notes that the isolated human "MSCs" (which are the same MSCs of Woodbury) are a heterogeneous population with at least two types of cells. In particular, Azizi notes "However, two distinct populations were seen, large flattened cells and relatively elongated or spindle shaped cells (Fig. 2a and b)." *See*, **Exhibit 9**; Azizi, page 3911, left col., last full paragraph. Azizi also characterizes their cell population (*i.e.*, Woodbury's cell population) as changing morphology in culture with continued passaging. *Id.* The human "MSCs" of Azizi also *require* cell culture supplementation with PDGF-AA to enhance cell growth and proliferation. *Id.* at page 3911, left col., first paragraph. The "hMSCs" of Azizi (*i.e.*, same as those of Woodbury) also have a population doubling time (PD) of about, at best, approximately 96 hours *with* PDGF-AA supplementation. *Id.* at page 3909, Fig. 1.

The significance of these attributes compared to the claimed cell populations are discussed further below.

2. The Examiner has not established a* prima facie *case of anticipation

Pending claims 14, 21, 25, 26 and 97 stand rejected under 35 U.S.C. § 102(b) as allegedly inherently anticipated by Haynesworth "taken in light of" Pittenger, Lee, and

Woodbury. *See*, **Exhibit 3**; Final Office Action, page 6, last paragraph to page 11, first paragraph. In view of these publications, the Examiner concludes "While the prior art does not clearly disclose all of applicant's claimed limitations, *it would appear*, that the cells claimed are a population of MSCs as disclosed by Haynesworth," *See*, **Exhibit 3**; Final Office Action, page 9, last paragraph (emphasis added).

Appellants respectfully submit that the Examiner's rejection under 35 U.S.C. § 102(b) is legally incorrect and should be reversed because the Examiner has not established a *prima facie* case of anticipation. In particular, the Examiner provides no basis for concluding that each and every element of the claimed invention is *necessarily present* in the prior art. Instead, the Examiner's rejection *is based on a mere possibility* that the claimed cell populations "would appear" to be "a population of MSCs as disclosed by Haynesworth." Mere possibility does not meet the requisite standard for making an inherent anticipation rejection. *See, Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002); *see also Electro Medical Sys., S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1052 (Fed. Cir. 1994) ("'The mere fact that a certain thing *may result* from a given set of circumstances is insufficient to prove anticipation...'") (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (emphasis added).

Furthermore, the only explanation the Examiner provides in support of his conclusion is:

> Something that is old does not become patentable upon the discovery of a new property, use, or application. Even if applicants had identified properties of the MSCs of Haynesworth et al. that Haynesworth et al. did not or could not test for, in this case the cells' telomerase expression level and ability to differentiate to various cell lineage types, such an identification would not render the MSCs of Haynesworth et al. patentable.

See, **Exhibit 3**; Final Office Action, page 9, last paragraph to page 10 first paragraph. Appellants are at a complete loss with respect to the Examiner's reference to telomerase expression level and cell differentiation properties because these elements are not limitations in any of the pending claims (nor were they when the Examiner last considered the claims and issued the final office action). Second, neither the claimed cell populations nor limitations within the claims represent a "new property, use, or application" *of Haynesworth's cells.* Instead, the claims are drawn to completely new and unique isolated cell populations.

Thus, Appellants respectfully submit that the Final Office Action rejection is based on mere conjecture and speculation by the Examiner without any extrinsic evidence, basis in fact, or technical reasoning provided to reasonably support his assertions. Moreover, and in contrast

to the Examiner's unsubstantiated conjecture, Appellants have previously, and again herein, provide evidence that the prior art cell populations of Haynesworth *are not the same* as the isolated cell populations of the presently claimed invention.

3. Differences between claimed invention and prior art

a) The cell populations of claims 14, 21, 25, 26 and 97 are not the same as those described in Haynesworth (U.S. Patent No. 5,733,542)

Claim 14, the main independent product claim, is as follows:

> An isolated cell population derived from human bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, and wherein the cell population maintains a doubling rate of less than about 30 hours after 30 cell doublings.

The Appellants previously provided the Examiner with evidentiary exhibits and an affidavit by Dr. Gene Kopen explaining why, and providing evidence that, the claimed cell populations, such as those encompassed by claim 14, are not the same as those described in Haynesworth, Pittenger, Lee or Woodbury. *See*, **Exhibit 8**; ("Second Kopen Declaration").

i) Haynesworth's MSCs have longer population doubling times and diminished self-renewal capacity compared to the claimed cell populations.

As an initial matter, a journal publication (co-authored by Stephen Haynesworth), describes characteristics of Haynesworth's MSCs which are highly relevant to the claims on appeal, but which are not explicitly described in the Haynesworth patent. *See*, **Exhibit 10**; Bruder, Jaiswal & Haynesworth, "Growth Kinetics, Self-Renewal, and the Osteogenic Potential of Purified Human Mesenchymal Stem Cells During Extensive Subcultivation and Following Cryopreservation," *Jour. Cell. Biochem.* 64:278-294 (1997)(hereinafter "Bruder" **(Exhibit 12)**).[5] Among characteristics discussed, the MSCs of Haynesworth are described in Bruder as: 1) acquiring increasingly longer population doubling times with each passage in culture; and, 2)

[5] The methods used in obtaining the MSCs in Bruder *et al.* are the same as described in Haynesworth. *Compare*, Haynesworth, Example 1, col. 3, line 57 to col. 4, line 51 *and* Caplan '359 Example 1, col. 17, lines 7-45 *with* Bruder, page 279, right col., last paragraph to page 280, left col., first paragraph. Appellants also note that each of the authors in Bruder are affiliated with Case Western Reserve University ("Case Western") and/or Osiris Therapeutics, Inc. ("Osiris"). Moreover, the Haynesworth and Caplan '359 patents were both assigned from each of the inventors to Case Western and from Case Western to Osiris. *See*, http://assignments.uspto.gov/assignments/?db=pat

having an average self-renewal capacity of only 38 +/- 4 population doublings (with the cells, thereafter, "degenerating"). *See, for example*, **Exhibit 12**; Bruder at: page 278 (Abstract); page 284, left col., second paragraph; page 284, right col., last paragraph to page 285, left col., first paragraph; and, page 285, left col., last paragraph.

According to Bruder the population doubling times of Haynesworth's MSCs become progressively longer with each passage in culture. *See*, **Exhibit 8**; Second Kopen Declaration, Section B.4, pages 8-11 (including calculations provided therein). Moreover, Haynesworth's MSC population doubling times are both initially, and subsequently, longer than 30 hours/population doubling (with doubling times ranging from ~54 to more than 100 hours/doubling). *See*, **Exhibit 8**; Second Kopen Declaration, Section B.4., pages 8-11. In contrast, the claims on appeal require a doubling rate of less than about 30 hours after 30 cell doublings. Thus, Haynesworth's MSCs have substantially different properties compared to the presently pending claimed cell populations.

ii) The claimed cell populations and the cell populations described in Haynesworth express different cell surface markers.

As explained above in the Summary of Cited References, the cell populations of Haynesworth are negative for expression of the cell surface marker CD44. By comparison, and as explained and evidenced via the Second Kopen Declaration, the isolated cell populations of the present invention are CD44 positive. *See*, **Exhibit 8**; Second Kopen Declaration, Section B.1, pages 3-4 *citing* the First Kopen Declaration (**Exhibit 2**; Section B.2(a), page 5 (including Exhibit B cited therein)). Hence, although expression of CD44 is not a limitation of the presently pending claims, *the inherent expression of this marker* by isolated cell populations of the present invention, *in contrast to the inherent lack of expression of this marker* in Haynesworth's cell populations, shows that these two cell populations are not the same.6

iii) The claimed cell populations and the cell populations of Haynesworth are obtained from different sub-populations of bone marrow cells.

In addition to differences in expression of CD44, the Second Kopen Declaration also provides explanation and evidence that the claimed cell populations and the cell populations of

[6] It is not necessary for Appellants' claims to include any further limitation over that of the claimed doubling rate of less than about 30 hours after 30 population doublings because this parameter alone is sufficient to distinguish the claimed cell populations over those of Haynesworth *et al* and others.

Haynesworth are found in, or obtained from, different sub-populations of bone marrow-derived cells. In particular, Haynesworth's "MSC" cell populations are isolated from among *a low density gradient fraction* of cells. *See*, **Exhibit 8**; Second Kopen Declaration, Section B.2, pages 4-6. In contrast, the gradient fractionation procedure in the present application teaches that Appellants bone marrow-derived cell populations are isolated from among a *high-density mononuclear cell fraction*. *See*, Specification, Example 2, page 27, lines 9-19 (emphasis added). Moreover, as explained in the Second Kopen Declaration, the different gradient fractionation mediums used by Haynesworth (70% Percoll for isolation of low density cell types) and that used in the present application (Histopaque 1.119® for isolation of high density cell types), could *not* be used to isolate the same starting cell populations because of the substantial differences in the separation properties of these media (*i.e.*, separation of high density versus low density cell types). *See*, **Exhibit 8**; Second Kopen Declaration, Section B.2., pages 4-5 including Exhibit B (cited therein). Hence, cell populations isolated from these different density gradient fractions represent different starting populations of cells even before any subsequent seeding, plating, or culturing procedures are implemented.

iv) **In vivo, *Haynesworth's "MSC" is a much rarer type of cell compared to the claimed cell populations.***

Haynesworth's "MSCs" represent a very rare cell type, *in vivo*, compared to cells of the claimed cell populations. The Haynesworth patent specification teaches "Although [MSCs] are normally present at *very low frequencies* in bone marrow and other mesenchymal tissues, the inventors of the present invention have discovered a process for isolating, purifying, and greatly replicating the mesenchymal stem cells in culture, *i.e. in vitro*." *See*, **Exhibit 4**; Haynesworth, col. 1, lines 25-29 (emphasis added). More particularly, Caplan '359 teaches that "MSCs" (*i.e.*, the same "MSCs" of Haynesworth) are present in bone marrow at a frequency of only about 1 in every 10,000 to 2,000,000 cells. *See*, **Exhibit 10**; Caplan '359, col. 4, lines 24-34.

The *in vivo* scarcity of Haynesworth's "MSCs" is significant because, as explained in the Second Kopen Declaration, Haynesworth's "MSCs" are present in bone marrow at a frequency that is approximately 500-3,000 fold *lower* than the *in vivo* frequency of cells used to produce the presently claimed cell populations. In particular, Caplan '359 teaches that "MSCs" are found in the low density fraction of cells at a concentration of about 50-500 "MSCs" per 30-50 x 10^6 nucleated cells (*i.e.*, a frequency of about 0.001% to 0.00016 % "MSC" per nucleated cell). *See*, Caplan '359, col. 10, lines 5-9. In contrast, the isolated cells of the present invention are found

in high density mononuclear cell gradient fractions at concentrations of about 1 cell in every 200 nucleated cells (*i.e.*, a frequency of about 0.5% cells per nucleated cell). *See*, **Exhibit 8**; Second Kopen Declaration, pages 4-5, section B.2, including footnote 1 and Exhibit E.

Hence, the much greater *in vivo* abundance of cells that are used to generate the cell populations of the present invention, compared to the relative *in vivo* scarcity of Haynesworth's "MSCs," is another factor which demonstrates that the claimed cell populations are not inherently the same as the "MSCs" of Haynesworth.

v) The "MSCs" of Haynesworth require specific media critical to their isolation and which is different from that used for isolation the claimed cell populations.

Isolation of Haynesworth's cell populations requires specific media which is described as "critical" for selective isolation of their "MSCs" cell population. As explained above, Haynesworth and Caplan '359 are related patents (continuations-in-part of the same parent application) which describe identical procedures for isolation and cultivation of MSCs. Unlike Haynesworth, the more extensive written description in Caplan '359 describes three specific types of media taught as "critical" for the selective adherence of "MSCs." *See*, Caplan '359, col. 6, line 45 through col. 9, line 35; *see also*, **Exhibit 8**; Second Kopen Declaration, Section B.3., pages 6-8 including Exhibit C (cited therein).

Media that can be used to isolate and culture the claimed cell populations, however, is different and distinct from the three "critical" types of media described for use in isolating Haynesworth's "MSCs." *See*, **Exhibit 8**; Second Kopen Declaration, Section B.3., pages 6-8 including Exhibit C (cited therein). Therefore, given the teachings in Caplan '359 regarding the critical nature of the defined media developed for selective adherence and isolation of the "MSCs" of Haynesworth, it is mere conjecture and speculation to suppose that Appellants' media might also allow for isolation and propagation of Haynesworth's cell populations. In other words, since the step that is described as "critical" for isolating the "MSCs" of Haynesworth, is not the same as that used to isolate cell populations of the claimed invention, it is highly unlikely (on this basis alone) that the cell populations of Haynesworth are the same as those of the present invention.

In sum, as demonstrated via the Second Kopen Declaration, the MSCs of Haynesworth differ from the claimed cell populations by virtue of, at least, differences in cell population doubling times, differences in cell surface marker expression, differences in bone marrow sub-

populations from which the cells can be obtained, and differences in cell culture media requirements.[7] Hence, the claimed cell populations are not inherently anticipated by Haynesworth.

b) The claimed cell populations are not the same as those described in Pittenger

The Examiner alleges that the claims are anticipated by Haynesworth in view of Pittenger and states that Pittenger is "cited as evidence that the MSC's of Haynesworth *et al.* can differentiate to various mesodermal cell lineages, including bone, cartilage, and adipose (Figure 2)." *See*, **Exhibit 3**; Final Office Action, page 7, fourth paragraph.

Regardless of whether or not the cells of Haynesworth can differentiate into bone, cartilage, and adipose cell types, Appellants' claimed cell populations and Haynesworth's MSCs are different cell populations (as discussed above). Therefore, Haynesworth does not anticipate the pending claims in view of Pittenger (or any other reference).

For the sake of thoroughness, Appellants submit that the presently pending claims are also not anticipated in view of Pittenger, with or without Haynesworth. In particular, as discussed in the Second Kopen Declaration, Pittenger describes an isolated population of cells which are *CD106 positive*. *See*, **Exhibit 5**; Pittenger, page 144, left col. ("These expanded attached mesenchymal cells were uniformly positive for...CD106... No subpopulations of marrow derived mesenchymal cells could be discerned morphologically by microscopic observation or by fluorescence cytometry, size, and granularity criteria or with more than 50 available antibodies..."). Furthermore, the cells described in Pittenger are also *CD62L positive*. *See*, **Exhibit 8**; Second Kopen Declaration, Section C, pages 12-13 (including Exhibit E; "Supplemental Web data" cited in Pittenger).

In contrast, as demonstrated in the Second Kopen Declaration, the isolated cell populations of the present invention are *CD106 and CD62L negative*. *See*, **Exhibit 8**; Second Kopen Declaration, Section C, pages 12-13 (including Exhibit D cited therein). Hence, although CD106 and CD62L expression is not a recited limitation of the claims on appeal, the difference in expression of these markers in cell populations of the present invention compared to those in Pittenger shows that these are two different cell populations.[8] Hence, Pittenger does not inherently anticipate the presently claimed cell populations (nor does Haynesworth in view of Pittenger).

[7] *See*, footnote 4.

[8] *See*, footnote 4.

c) The claimed cell populations are not the same as those described in Lee

The Examiner alleges the claims are anticipated by Haynesworth in view of Lee, and asserts that Lee is "cited as evidence that the MSCs of Haynesworth *et al.* can differentiate to hepatocytes...". *See*, **Exhibit 3**; Final Office Action, page 7, sixth paragraph. Regardless of whether or not the cells of Lee can differentiate into hepatocytes, Appellants' claimed cell populations and Haynesworth's "MSCs" are not the same. Therefore, Haynesworth does not anticipate in view of Lee (or any other reference).

For the sake of thoroughness, Appellants submit that the claims are not anticipated in view of Lee. In particular, the cell populations described by Lee have substantially longer doubling times than the claimed cell populations. Lee states "The doubling time of these BM-derived cells was found to be between 40 to 52 hours (data not shown)." *See*, Lee at page 1278, right col., 1st paragraph. In contrast, the claimed cell populations maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

Further, as explained in the Second Kopen Declaration, Lee describes a population of cells which are *CD13 negative*. *See*, **Exhibit 8**; Second Kopen Declaration, Section D, page 13 *citing* Lee at page 1278, right col. ("The fibroblast-like morphology of BM-derived cells...as well as their surface phenotype (Fig. 1B), as determined by flow cytometry, were consistent with those reported in the literature for MSCs [*citing* Pittenger, *Science* 1999; *284*:143-147]. These BM-derived *cells were negative for CD13*...") (emphasis added)). In contrast, as demonstrated by the Second Kopen Declaration, the isolated cell populations of the present invention are *CD13 positive*. *See*, **Exhibit 8**, Second Kopen Declaration, Section D, page 13, including Exhibit D referenced therein. Hence, although CD13 expression is not a limitation of the presently claimed cell populations, the difference in expression of this marker in cell populations of the present invention compared to the cell populations described in Lee shows that these are different cell populations. Hence, Lee does not inherently anticipate the presently claimed cell populations.[9]

Therefore, the isolated cell populations of the present invention are not the same, nor are they essentially the same, as the cell populations described in Lee. Accordingly, the claimed cell populations are not inherently anticipated by Lee, nor by Haynesworth in view of Lee.

[9] *See*, footnote 4.

d) The claimed cell populations are not the same as those described in Woodbury

The Examiner alleges the claims are anticipated by Haynesworth in view of Woodbury. In particular, the Examiner states that Woodbury is cited as "evidence that the MSCs of Haynesworth et al. can differentiate to neurons." *See*, **Exhibit 3**; Final Office Action, page 7.

As detailed in the *Summary of Cited References* (above), the human "MSCs" described in Woodbury are the same as those described in Azizi *et al.*, *Proc Natl Acad Sci USA*. 95:3908-3913 (1998) (hereinafter "Azizi" (**Exhibit 9**)). Moreover, with significance to the claims on appeal, the "MSCs" of Azizi (and, therefore, of Woodbury) have a population doubling time (PD) of about, *at best, approximately 96 hours with PDGF-AA supplementation. See*, **Exhibit 9**; Azizi, page 3909, Fig. 1; showing cell number at Day 0 = $9x10^4$ cells, which approximately double, with PDGF-AA supplementation, to ~$18x10^4$ cells by Day 4 (*i.e.*, 96 hours later). In contrast, the claimed cell populations have a doubling rate of less than about 30 hours after 30 cell doublings. Hence, the "MSCs" of Woodbury do not inherently anticipate the claims on appeal.

Furthermore, the isolated "MSCs" of Azizi (and, therefore, of Woodbury) are a heterogeneous population with at least two types of cells. In particular, Azizi notes "However, two distinct populations were seen, large flattened cells and relatively elongated or spindle shaped cells (Fig. 2a and b)." *See*, **Exhibit 9**; Azizi, page 3911, left col., last full paragraph. Azizi also characterizes their cell populations as changing morphology in culture with continued passaging in the same manner as discussed (*above*) in Bruder *et al.* (*i.e.*, same as for the "MSCs" of Haynesworth). *See*, Azizi, page 3911, left col., last full paragraph ("As noted previously (see ref. 24 [Bruder *et al.*]), the human MSCs became relatively homogeneous in appearance as the cells were passed"). In contrast, as explained in the *Summary of the Claimed Subject Matter* (above), cell populations of the invention are uniform and homogenous populations of cells exhibiting stable and constant growth characteristics.

Azizi also describes their "MSCs" as requiring cell culture supplementation with PDGF-AA for optimal growth. For example, the "MSCs" of Azizi require supplementation with PDGF-AA merely to grow sufficient quantities of the cells to perform the experiments described therein. *See*, **Exhibit 9**; Azizi, page 3911, left col., first paragraph ("As indicated in Fig. 1, addition of PDGF-AA increased the growth rate of the cells. Therefore PDGF-AA was added to passages 2-5 to obtain adequate numbers of human MSCs for the experiments here"). In contrast, as evidenced by the First Kopen Declaration (**Exhibit 2**; Section D.3., page 18) the

cell populations of the present invention do not require supplementation with growth factors (such as PDGF-AA or others) to maintain consistently rapid and continuous population doubling rates.

Accordingly, given the slow population doubling times, the requisite need for growth factor supplementation, the presence of at least two distinct cell types, and the changing morphology of the cell populations with continued passaging, it is clear that the MSCs of Woodbury are not the same, nor are they essentially the same, as the claimed cell populations. Thus, the claimed cell populations are not inherently anticipated by the MSCs of Woodbury, nor by the MSCs of Haynesworth in view of Woodbury.

4. Summary and Conclusion: Inherent Anticipation – Haynesworth, Pittenger, Lee, and Woodbury

The claims on appeal are not inherently anticipated by Haynesworth alone, or "taken in light of" view of Pittenger, Lee, or Woodbury. In particular, as discussed and demonstrated above:

- Haynesworth's MSCs have significantly longer (ranging from ~54 hours to more than 100 hours) and acquire increasingly slower population doubling times compared to the claimed isolated cell populations, which maintain a doubling rate of less than about 30 hours after 30 cell doublings.
- Haynesworth's MSCs are CD44 negative, whereas the isolated cell populations of the present invention are inherently CD44 positive.
- Haynesworth's MSCs are isolated from among a low density, platelet-containing fraction of cells in a 70% Percoll (low density) gradient, whereas cell populations of present invention are isolated from among a high density, mononuclear cell-containing fraction in a Histopaque 1.119® (high density) gradient. Thus, starting cell populations obtained from two *physiologically distinct* cell sub-populations indicates the isolation of non-identical cell types.
- Haynesworth's "MSCs" are present *in vivo* at much lower concentrations than the cells that produce cell populations of the present invention.
- Isolation of Haynesworth's "MSCs" is described as critically reliant on one of three-types of specific cell culture media, each of which are

different from media used in isolating the cell populations of the present invention.

Accordingly, Appellants have demonstrated by explanations and evidence that the cell populations of the invention are not inherently the same "MSCs" as described by Haynesworth et al. Therefore, Appellants respectfully request that the Board reverse the Examiner's rejection of claims 14, 21, 25-26 and 97 under 35 U.S.C. § 102 (b).

5. Dependent Claim 21 is further not anticipated

Claim 21 is drawn to:

> The isolated cell population of Claim 14, further including expression of p21 or p53 after between about 20 to about 50 population doublings of the cells, wherein expression of p53 is a relative expression of up to about 3000 transcripts of p53 per 106 transcripts of an 18s rRNA and expression of p21 is a relative expression of up to about 20,000 transcripts of p21 per 106 transcripts of an 18s rRNA.

Appellants submit that claim 21 is not inherently, or otherwise, anticipated by Haynesworth because claim 21 depends from claim 14, and claim 14 is not anticipated by Haynesworth for the reasons provided above. Further, claim 21 is not anticipated by Haynesworth (with or without Pittenger, Woodbury and/or Lee) because none of these references teach or describe cell populations with having the claimed parameters pertaining to expression of p21 or p53 after between about 20 to about 50 population doublings.

The references to Pittenger, Woodbury, and Lee are irrelevant because claim 21 makes no reference to the isolated cell populations' ability to differentiate into bone, cartilage, adipose, neurons and hepatocytes. Appellants have also demonstrated herein that the claimed cell populations are not inherently, or otherwise, anticipated by Pittenger, Woodbury or Lee of their own accord (*i.e.*, with or without Haynesworth). Finally, these three references are also irrelevant to alleged inherent anticipation by Haynesworth because (as explained above) Haynesworth itself does not inherently, or otherwise, anticipate claim 21.

Appellants respectfully request that the Board reverse the rejection of claim 21 under 35 U.S.C. 102(b).

6. Independent Claim 97 is further not anticipated

Claim 97 is a product-by-process claim drawn to:

> An isolated cell population obtainable from human bone marrow by steps that comprise:
>
> a) incubating human bone marrow cells under a low oxygen condition such that said cells when allowed to adhere to a tissue culture-treated surface will produce adherent colony forming units (CFU); and,
>
> b) passaging cells in said adherent CFU at a seeding density of less than about 2500 cells/cm^2,
>
> wherein greater than about 91% of said passaged cells co-express CD49c and CD90, and wherein said passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

Appellants submit that claim 97 is neither explicitly nor inherently anticipated by Haynesworth for the reasons provided above. In particular, as demonstrated by the evidence submitted herein, the claimed cell populations are not inherently anticipated by Haynesworth because Haynesworth's cell populations do not maintain a doubling rate of less than about 30 hours after 30 cell doublings (as required by claim 97).

Furthermore, claim 97 is also not anticipated by Haynesworth (with or without any one or all of Pittenger, Woodbury, and Lee) because none of these references teach or describe the claim limitations of incubating and passaging a population of bone marrow-derived cells under a combination of low oxygen *and* low cell seeding density conditions.

Since these steps are not used in the prior art and since, to the best of Appellants' knowledge, these steps are necessary to produce the claimed product (*i.e.,* human bone marrow-derived cell populations wherein greater than about 91% of the cells co-express CD49c and CD90, and wherein said passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings), it is impossible that the cell populations described in the cited prior art are the same as those of claim 97. As stated previously, a rejection based on inherent anticipation must be based on more than mere possibilities or probabilities. The outstanding rejection does not lead to recognition by one of skill in the art that the processes in the cited prior art will necessarily lead to the cell populations of claim 97. In contrast, as demonstrated by the evidence provided herein, Appellants have shown that the bone marrow-derived cell populations isolated according to the prior art methods *do not* produce the cell populations of claim 97 (such as, for example, cell populations wherein the passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings.)

Appellants' claimed cell populations are also not inherently anticipated by Haynesworth's cell populations because each *are inherently different cell populations*. As demonstrated, for example, by differences in expression of CD44 (*negative* for Haynesworth's cell populations, *positive* for Appellants' cell populations), by differences in the physical cell density of the cell sub-populations from which they can be obtained, and by differences in cell culture media requirements.

The references to Pittenger, Woodbury, and Lee are irrelevant because claim 97 makes no reference to the isolated cell populations' ability to differentiate into bone, cartilage, adipose, neurons and hepatocytes. Appellants have also demonstrated herein that the claimed cell populations are not inherently, or otherwise, anticipated by Pittenger, Woodbury or Lee of their own accord (*i.e.*, with or without Haynesworth). Finally, these three references are also irrelevant to alleged inherent anticipation by Haynesworth because (as explained above) Haynesworth itself does not inherently, or otherwise, anticipate claim 97.

Appellants respectfully request that the Board reverse the rejection of claim 97 under 35 U.S.C. 102(b).

D. The rejection of claim 97 under 35 U.S.C. § 112, first paragraph, is incorrect and should be reversed

The Examiner finally rejects claim 97 under 35 U.S.C. § 112, first paragraph, as allegedly "failing to comply with the written description requirement." The Examiner states that "New claim 97 is rejected for containing new matter" because "[t]he examples cited for support do not contain the limitation of a seeding density of 'less than about 2500 cells/cm^{2}' and in fact Example 1 differs greatly from the claimed invention despite the fact that the method in Example 1 is alleged to be the method which produces the claimed cell population." *See*, **Exhibit 3**; Final Office Action, page 5, first and second paragraphs. Appellants respectfully disagree and herein address each of these two allegations in turn.

1. 2500 cells/cm^{2}

The critical aspects necessary for isolating, culturing, and propagating cell populations of the claimed invention are culturing cells using *low cell density seeding* (such as, for example, at less than about 2500 cells/cm^{2}) *under low oxygen conditions*. *See, e.g.*, **Exhibit 1**; Specification,

page 11, line 27 to page 12, line 9. Hence, original claim 97 does not "differ greatly from the claimed invention" because it incorporates both of these two essential elements as necessary limitations of this product-by-process claim.

Furthermore, original claim 97 does not contain new matter and does not lack written description support. The specification does, in fact, teach "a seeding density of less than about 2500 cells/cm^2." *See*, for example, **Exhibit 1**; Specification at page 11, line 12 to page 12, line 5; and, Examples 1 through 4, page 25 to page 30. The Examiner has apparently overlooked or ignored page 12, lines 4-5 which states "Bone marrow cell expansion is conducted with a seeding density of less than about 2500 cells/cm^2...."

Accordingly, the rejection of claim 97 under 35 U.S.C. § 112, first paragraph, based on an alleged lack of written description is factually and legally incorrect and should be reversed.

2. The Method of Example 1

It is *not* Appellants' position that the method of Example 1 is "the method which produces the claimed cell population." Both Examples 1 and 2 are part of the process of producing cell populations of the present invention. The key distinction between Examples 1 and 2 is that they describe two different means by which a starting population of cells may be obtained (*i.e.*, either by ammonium chloride lysis of red blood cells in a whole bone marrow aspirate and subsequent plating and culturing of the remaining cells (Example 1) or by gradient fractionation of a whole bone marrow aspirate, followed by plating and culturing of fractionated mononuclear cells (Example 2)). Indeed, *either of these methods* can be used, non-exclusively, to obtain a *starting* source population of the claimed cell populations.

Hence, the Examiner's assertion that the specification does not contain adequate written description under 35 U.S.C. § 112, first paragraph, for the claim 97 limitation "of a seeding density of 'less than about 2500 cells/cm^2'" is factually and legally incorrect.

In view of the above, Appellants request that the Examiner's rejection of claim 97 under 35 U.S.C. § 112, first paragraph, be reversed.

E. The rejection of claim 97 under 35 U.S.C. § 112, second paragraph, is incorrect and should be reversed

Claim 97 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner rejects claim 97 as indefinite based on the recitation of

"low oxygen" allegedly because "it is unclear what the intended metes and bounds of a 'low oxygen' condition are." *See*, **Exhibit 3**; Final Office Action, pages 5, last two paragraphs. The Examiner mischaracterizes the teachings of the present application in this regard by stating:

> Applicant's function [sic, functional?] definition (see applicants [sic] examples) of low oxygen would seem to encompass a range from 5% oxygen to about 23% oxygen (an concentration [sic] greater than the concentration of oxygen in air) as applicant's function definition [sic] encompasses a 90% air/5% oxygen composition and as such would not appear to define a "low oxygen" concentration at all.

See, **Exhibit 3**; Final Office Action, page 6, first paragraph.

As an initial matter, Appellants are at a complete loss as to where the Examiner derived the figure he alleges for a low oxygen range up to "about 23%."

Second, the specification clearly provides the following definition: "'Low oxygen condition,' as used herein, refers to a concentration (*e.g.*, percent of oxygen based on volume, weight or molarity) which is *less than atmospheric oxygen*." *See*, **Exhibit 1**; Specification, page 14, lines 21-23. Further, the specification explicitly describes low oxygen concentrations ranging from 1% to "less than atmospheric" (and not 5% to about 23% as alleged by the Examiner).

For example, the specification teaches:

- "(*e.g.*, a low oxygen concentration such as about 5% oxygen)."

See, **Exhibit 1**; Specification, page 8, lines 11-12.

- "Bone marrow aspirates, or a cellular fraction of the aspirate, are cultured at a dissolved oxygen concentration of less than about 20%, preferably between about 1% to about 10%, and most preferably from between about 2% oxygen to about 7% oxygen. In a preferred embodiment, the dissolved oxygen concentration is about 5% oxygen."

Id. at page 11, line 27 to page 12, line 1.

- "In one embodiment, the source of the cell population is cultured under a low oxygen condition (*e.g.*, less than atmospheric). "Low oxygen condition," as used herein, refers to a concentration (*e.g.*, percent of oxygen based on volume, weight or molarity) which is less than atmospheric oxygen."

Id. at page 14, lines 20-23.

- "In a preferred embodiment, the low oxygen condition is an oxygen concentration less than about 15% oxygen, and more

> preferably an oxygen concentration less than about 10%, and most preferably an oxygen concentration of about 5% oxygen."

Id. at page 15, lines 6-11.

The Examiner also incorrectly states that "applicant's function definition [sic] encompasses a 90% air/5% oxygen composition." *See*, **Exhibit 3**; Final Office Action, page 6, first paragraph. The Examiner has misconstrued the Examples section of the specification which states that cells were incubated "in an atmosphere consisting of 5% carbon dioxide, 5% oxygen, and 90% nitrogen/air." Appellants are at a loss to understand why the Examiner elected to modify this sentence to imply a composition of "90% air/ 5% oxygen composition" (instead of air at 5% carbon dioxide, 5% oxygen, and 90% nitrogen).

In sum, Appellants submit that original Claim 97 is not indefinite. Therefore, Appellants request that the Examiner's rejection of claim 97 under 35 U.S.C. § 112, second paragraph, be reversed.

F. The objection to the amended specification should be rendered moot.

The Examiner objected to an amendment in the specification as introducing new matter. *See*, **Exhibit 3**; Final Office Action, page 6, second paragraph. On June 16, 2009, Appellants re-submitted this amendment for further consideration with a Petition under 37 C.F.R. § 1.181 **(Exhibit 13)**. Appellants' Petition was denied in a Decision mailed on July 14, 2009 **(Exhibit 14)**.

To comply with the Decision on the Petition, Appellants submitted an Amendment Under 37 C.F.R. § 1.116 (b)(3) to cancel the allegedly new subject matter **(Exhibit 15)**. Appellants note that this amendment could not have been introduced earlier because the first objection to the alleged new matter was not asserted by the Examiner until mailing of the currently pending final office action and Appellants only thereafter were able to obtain a subsequent disposition from the U.S.P.T.O. in view of Appellants' Petition under 37 C.F.R. § 1.181.

On December 24, 2009 the Examiner mailed an Advisory Action refusing to enter the above-referenced amendment in the specification (*i.e.*, to cancel allegedly new subject matter).

Accordingly, Appellants herein request that the requested amendment of the specification submitted under 37 C.F.R. § 1.116 (b)(3) on August 17, 2009 be considered and entered, thereby rendering the Examiner's objection to the specification moot.

G. Provisional Double Patenting Rejection

The Examiner states a provisional non-statutory double patenting rejection of claims 14, 21, 25, 26 and 97 based on the co-pending, *later filed* 10/251,685 application. *See*, **Exhibit 3**; Final Office Action, pages 11-13.

Appellants respectfully request that the asserted double patenting rejection be held in abeyance until claimed subject matter is deemed allowable, at which time Appellants will consider filing a terminal disclaimer in the later issued patent in compliance with 37 C.F.R. §§ 1.321(c) or 1.321 (d) in the later filed Application No. 10/251,685 to overcome the double patenting rejection of claims 14, 21, 25-26 and 97.

H. Appellants' Remarks on Non-Statutory Comments By the Examiner

In the Final Office Action, the Examiner sets forth approximately three pages of subjective comments, improperly asserting reasons generally rejecting the pending claims *without citing any statutory basis* under which the asserted rejections are to fall and without distinguishing which claims such assertions are alleged to apply. *See*, **Exhibit 3**; Final Office Action, pages 2-4. Appellants submit that these comments do not provide an appropriate or valid basis for rejecting the pending claims (as required pursuant to 35 U.S.C. § 1.132). Furthermore, the lack of any cited statutory basis in relation to these comments deprives Appellants of the ability to properly determine and distinguish pertinent issues in order to counter alleged grounds of rejection. *See e.g., Chester v. Miller*, 906 F.2d 1574, 1578 (Fed. Cir. 1990) ("[35 U.S.C.] Section 132...ensures that an applicant 'at least be informed of the broad statutory basis for [the rejection of] his claims, so that he may determine what the issues are on which he can or should produce evidence...' Section 132 is violated when a rejection is so uninformative that it prevents the applicant from recognizing and seeking to counter the grounds for rejection." (citations omitted)).

Therefore, Appellants submit that since the Examiner's commentary in this section of the Final Office Action is not associated with any particular patent statutes or judicial doctrines, these comments should be disregarded by the Board of Patent Appeals and Interferences.

Appellants note, however, that where portions of the Examiner's comments in this section were repeated in subsequent parts of the Final Office Action, in association with specific claims and statutory grounds, Appellants *have* specifically addressed such comments and

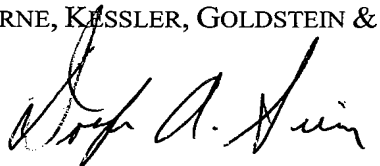
rejections (as indicated and presented in the arguments and evidence submitted above and included in the exhibits herewith).

VIII. Conclusion

For the reasons discussed above, Appellants respectfully submit that the rejections of claims 14, 21, 25, 26 and 97 under 35 U.S.C. § 102(b); § 112, first paragraph; and § 112, second paragraph are in error and should be reversed. Appellants request that these claims be allowed to issue. Furthermore, the objection under 35 U.S.C. § 132(a) to the previously submitted amendment is presently moot and Appellants request that the provisional double patenting rejection be held in abeyance until a favorable decision is rendered with respect to the presently pending claims.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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IX. Claims Appendix (37 C.F.R. § 41.37(c)(1)(viii))

14. An isolated cell population derived from human bone marrow, wherein greater than about 91% of the cells of the cell population co-express CD49c and CD90, and wherein the cell population maintains a doubling rate of less than about 30 hours after 30 cell doublings.

21. The isolated cell population of Claim 14, further including expression of p21 or p53 after between about 20 to about 50 population doublings of the cells, wherein expression of p53 is a relative expression of up to about 3000 transcripts of p53 per 10^6 transcripts of an 18s rRNA and expression of p21 is a relative expression of up to about 20,000 transcripts of p21 per 10^6 transcripts of an 18s rRNA.

25. The isolated cell population of Claim 14, wherein the cell population does not express CD34 and/or CD45.

26. The isolated cell population of Claim 14, wherein the cell population further expresses at least one trophic factor selected from the group consisting of BDNF, IL-6, NGF and MCP-1.

97. An isolated cell population obtainable from human bone marrow by steps that comprise:

a) incubating human bone marrow cells under a low oxygen condition such that said cells when allowed to adhere to a tissue culture-treated surface will produce adherent colony forming units (CFU); and,

b) passaging cells in said adherent CFU at a seeding density of less than about 2500 cells/cm^2,

wherein greater than about 91% of said passaged cells co-express CD49c and CD90, and wherein said passaged cells maintain a population doubling rate of less than about 30 hours after 30 cell doublings.

X. Evidence Appendix (37 C.F.R. § 41.37(c)(1)(ix))

Copies of the evidence relied upon by Appellants in this Appeal Brief are provided. The Table below sets forth the location of the evidence in the Record

Exhibit	Title of Exhibit	Location in Record
Exhibit 1	Specification	U.S. Patent Application No. 09/960,244 filed September 21, 2001.
Exhibit 2	First Kopen Declaration (including Exhibits A-D referenced therein).	Declaration of Gene Kopen Under 37 C.F.R. § 1.132 submitted in Appellants reply to a non-final office action on May 18, 2007.
Exhibit 3	Final Office Action	Final Office Action mailed Mar. 16, 2009 (Paper No. 20081220).
Exhibit 4	Haynesworth	U.S. Patent 5,733,542 cited by the Examiner in a non-final Office Action mailed Oct. 5, 2007 (Paper No. 20070930) and in the Final Office Action mailed Mar. 16, 2009 (Paper No. 20081220).
Exhibit 5	Pittenger	Pittenger *et al., Science 284*: 143-147 (1999) cited by Appellants in an Information Disclosure Statement as reference "AZ2" on Jan. 22, 2002 and resubmitted on Dec. 23, 2003; cited by the Examiner in a non-final Office Action mailed Oct. 5, 2007 (Paper No. 20070930) and in the Final Office Action mailed Mar. 16, 2009 (Paper No. 20081220).
Exhibit 6	Woodbury	Woodbury *et al., Journal of Neuroscience Research 61*:364-370 (2000) cited by the Examiner in a non-final Office Action mailed Oct. 5, 2007 (Paper No. 20070930) and in the Final Office Action mailed Mar. 16, 2009 (Paper No. 20081220).
Exhibit 7	Lee	Lee *et al., Hepatology 40*: 1275-1284 (2004) cited by the Examiner in a non-final Office Action mailed Oct. 5, 2007 (Paper No. 20070930) and in the Final Office Action mailed Mar. 16, 2009 (Paper No. 20081220).
Exhibit 8	Second Kopen Declaration (including Exhibits A-E referenced therein)	Declaration of Gene Kopen Under 37 C.F.R. § 1.132 submitted in Appellants reply to a non-final office action on March 5, 2008.

Exhibit	Title of Exhibit	Location in Record
Exhibit 9	Azizi	Azizi *et al.*, *Proc Natl Acad Sci USA.* 95:3908-3913 (1998) cited by Appellants in an Information Disclosure Statement as reference "AS" on Jan. 22, 2002 and resubmitted on Dec. 23, 2003.
Exhibit 10	Caplan '359	U.S. Patent No. 5,486,359 cited by Appellants in an Information Disclosure Statement as reference "AC" on Jan. 22, 2002 and resubmitted on Dec. 23, 2003.
Exhibit 11	Caplan '094	U.S. Patent No. 5,811,094 cited by Appellants in an Information Disclosure Statement as reference "AG" on Jan. 22, 2002 and resubmitted on Dec. 23, 2003.
Exhibit 12	Bruder	Bruder *et al.*, *Jour. Cell. Biochem.* 64:278-294 (1997) submitted by Appellants in reply to office action as Exhibit E on Dec. 22, 2003; cited again in Information Disclosure Statement submitted Mar. 5, 2008.
Exhibit 13	Petition under 37 C.F.R. § 1.181	Submitted by Appellants on Jun. 16, 2009.
Exhibit 14	Decision mailed on July 14, 2009	Office Communication mailed Jul. 14, 2009.
Exhibit 15	Amendment Under to 37 C.F.R. § 1.116	Submitted by Appellants on Aug. 17, 2009.

XI. Related Proceedings Appendix (37 C.F.R. § 41.37(c)(1)(x))

There are no decisions rendered by a court or the Board in related proceedings to provide at this time.